BIO-CHEMISTRY IN ITS RELATIONS TO NERVOUS DISEASES.

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THE last decade witnessed the definite beginnings of an important revolution in medicine, and the present is already bearing the practical fruits of its actual accomplishment. Thus rapidly do the wheels of change revolve in these closing hours of the nineteenth century. This revolution was not wrought amid musty tomes, nor even among the more pregnant volumes of hospital wards or general practice, but in the quiet retreat of laboratories, where the search-light of science was being focused upon many of the hitherto inscrutable phenomena of nature. We can scarcely be said to have advanced far in this pathless but fertile field, and yet enough has been learned as to so materially modify existing theories and facts that it constitutes a veritable revolution. It has already created a new pathology, and is at the present moment creating a new therapeutics.

It is my purpose briefly to advert to some of the more important bearings which this influx of knowledge is having, and bids fair to have, in the domain of nervous diseases.

*Read before the Mississippi Valley Medical Society at Detroit, September 4, 1895.

It is the merest platitude to remark that the nervous system not only controls, but is itself profoundly influenced directly or indirectly by, the functional processes and products of every organ and tissue of the body, and yet it seems expedient to emphasize the importance of this fundamental fact. The secretory function of the stomach, liver, or kidney, and the metamorphic changes of muscle, gland, or nervous tissue itself, may stimulate, inhibit, or pervert the function of the central or peripheral nervous mechanism. If it were necessary, as it probably is not, to cite illustrations in support of this proposition, I could mention the effect upon the nervous system of delayed digestion of a full meal, because of defective gastric secretion; of accumulated urea, because of defective renal function; or of excess of carbonic acid, or deficient oxidation owing to lung involvement. Perverted or foreign chemical products, or normal ones in excess or deficiency, may so modify the pabulum of nervous tissue as to more or less seriously influence its function.

On the other hand we have the functional products of microscopic organisms, the main source of supply of which is probably the digestive canal, finding their way by absorption into the general circulation, and thus reaching and influencing the nervous mechanism. The bacteriology of the digestive tract is one of the most fertile fields of contemporary research. Whenever its morphology and chemistry have been worked out, and experimental physiology, supported by clinical observation, has

solved the difficult problems relating to the physiological action of the various ptomaines, it will be more than a mile-stone—it will mark an era—in the progress of medicine. Its bearings in every department of both medical science and art are too obvious to require comment. The symptomatology of some essential fevers will from that moment stand upon a definite scientific basis, and receive a rational explanation. It will then be possible to make a careful study of the antidotal relations between ptomaines and drugs, or between certain ptomaines and other ptomaines, with great possibilities for the future of general therapeutics.

To the bacteriology of the digestive tract should be added that of the respiratory and genito-urinary tracts, which are of immense, though, with one or two notable exceptions, of subordinate, importance.

We have thus a wide series of bio-chemical products, of very diverse origin, which come in contact with the nervous system through the blood column, giving rise to pathological phenomena. There is not, so far as I know, any existing classification of these chemical products that will serve my purpose; so that I will venture the following tentative arrangement into six groups, based on their sources of origin:

(1) Bacteriological products or ptomaines;
(2) Products of perverted metamorphosis of tissue, including the leucomaines;
(3) Defective elimination of excretory organs;
(4) Perverted secretion of glandular organs;
(5) Products of imperfect digestion;

(6) Chemical compounds probably present in independent blood states, and of unknown origin.

A more scientific classification would be based upon their ultimate chemical analysis or physiological action, as determined by experimental study; but the data are not yet at hand.

Of course it is neither possible nor desirable to even briefly refer individually to all the various chemical products involved in this scheme. To discuss them fully would be to write a general treatise upon a special field in pathology. The entire arrangement is in fact schematic. Its complete justification will, perhaps, in part, have to rest upon the results of future investigation. It would be difficult in the present state of our knowledge, to establish the practical importance of some of the classes mentioned, although I feel convinced that careful reflection will give to each a strong degree of probability, as an etiological factor in nervous diseases, while the importance of others is not open to doubt.

As an indication of the influence of perverted secretion of glandular organs may be mentioned the mental depression and cephalalgia associated with hepatic jaundice. Uremic convulsions may fitly represent the effect of defective elimination. The lithemic diseases of the nervous system illustrate the results of the chemical products of perverted tissue-metamorphosis. Concerning independent blood states but little can be said at present. Too little is known of the chemistry of the blood. Yet there are many facts which indicate the existence

of chemical products in human blood as important as they are unknown. I might mention as pointing in this direction the investigations of Rummo and Bordini in which it was shown that about four drams of normal human blood-serum, when given by intravenous injection, will kill a rabbit weighing four pounds.

Exceedingly suggestive were their further observations that the serum from patients suffering from mania was found to be more toxic than that from patients suffering from depressed emotional states. These facts can only be explained by assuming the existence in the blood of potential, though at present unknown, chemical compounds.

The products of imperfect digestion, so far as we at present know are principally important because of their association with the group designated as bacteriological products or ptomaines, and by far the most important of all. Many are already known, and many undoubtedly remain to be discovered. Among the poisons of this type which have been already isolated, may be mentioned peptotoxin, typhotoxin, muscarine, neurine, etc. The isolation and study of the physiological action of these numerous chemical compounds, so many of which are constantly being formed in the intestinal canal, are among the most pressing needs of the hour; and while it cannot, perhaps, be at present asserted as a fully established fact, it is exceedingly probable, that some of their poisons will be found to have a selective affinity for certain parts of the nervous mechan-

ism; and their long-continued, constant action, provided for by their continuous production in the culture media of the alimentary canal, may easily give rise first, to vascular and so-called functional disturbances, later terminating in the various types of organic disease, heretofore regarded as spontaneous in their development, or, at least, of unknown origin.

Inasmuch as the theory of a special affinity of certain chemical poisons circulating in the blood for certain tissues is so very important from my point of view, it may be well for us to pause at this point and examine its plausibility.

This theory, as applied to organic chemical agents, finds a complete parallel in the action of certain minerals when taken into the circulation. Mercury, for instance, produces turgescence and swelling of the pancreas and salivary glands. We are familiar with the coryza of the iodides and the blue line of plumbism, as well as the extensor paralyses produced by the latter. Why is lead paralysis not found in the flexors or pronators, or ordinarily elsewhere than in the forearm? We might refer, on the other hand, to the well-known predilection which the diphtheria germ shows for the upper respiratory passages; Eberth's typhoid bacillus for Peyer's glands; and the exanthems for the skin. These and many other similar phenomena can only be explained upon the theory that, when certain chemical agents are taken into the circulation, they may pass by, as it were, many organs and tissues, perhaps all but one, and upon that one exert their peculiar physiological effect. In as-

suming, therefore, that the various chemical products derived from bacteriological processes, metabolism, etc., may, by a process of selection, exert a pathological influence, not only upon the nervous system, but upon certain sharply defined areas thereof—as in the system lesions of the cord, or involvement of certain nerves—we are fully supported by a strong group of analogous facts with which we are familiar, and which need only to be mentioned in order that their force can be fully seen.

Having pointed out the existence of these chemical poisons, and shown the reasonableness of the theory of their selective action upon the nervous system, let us proceed a step further, and make a cursory examination of a little of the evidence derived from clinical neurology itself, and also see to what extent these contentions are sustained by facts and theories already in a large measure established.

Let us first notice briefly one of the most common, as well as most hopelessly fatal, of organic nervous affections—locomotor ataxia. It seems to be fairly well established that a very large proportion of the cases of locomotor ataxia are produced by syphilis. According to some observers the proportion of cases in which this relation exists is as high a ninety per cent. The proportion conceded by nearly all clinicians, however, is altogether too large to be accidental. While admitting, therefore, and claiming that a certain, rather small minority of cases of locomotor ataxia are nonsyphilitic, I shall proceed upon the assumption

that the larger proportion are caused by this chronic infectious disease.

Now, syphilis is admittedly a microbial disease. But as is probably true of nearly all microbial diseases, it does not produce its pathological results by the direct action of the microbe upon the tissues. It is to the chemical products of their growth that we must look for the explanation. Just how these chemical poisons are produced is at present a mooted question. They may be a secretion or an excretion of the micro-organism. While, in some instances at least, the toxic properties of micro-organisms are not present in fluids containing them so long as the organisms are alive and the fluid acid, when they die and the fluid becomes alkaline it at the same time becomes highly toxic, indicating that the ptomaine is, in some cases at least, simply contained in the body of the organism, and is abstracted by post-mortem maceration in an alkaline medium. But be the explanation what it may, it can be fairly assumed as a fact established by analogy that syphilis produces its lesions by a chemical poison developed in some unknown manner by the bacillus causing the disease.

How, then, does this poison produce locomotor ataxia? Why does it not produce sclerosis of the crossed pyramidal tracts, or degeneration of the anterior cornua? Why does it not produce a multiple neuritis or a multiple sclerosis? Why d o e s it produce, instead of these, a degenerative disease, which, though not limited to the spinal cord, is, so far as the spinal-cord involvement is concerned, at least primarily limited to a

single area of its transverse section, known as Burdach's column.

The proximal answer to these questions is perfectly clear and obvious; the ultimate one will probably forever elude our search. We can only say that for some reason, utterly unknown to us, this syphilitic toxin, while passing through the circulation of the cord, and therefore necessarily coming in contact with every element of its structure, only exerts its baneful influence upon the histological elements of one of the several areas of its transverse section. There is, in other words, some sort of selective affinity, which we have found not to be a rare phenomenon of biological law, that determines the extent and limitations of the resulting lesions. These lesions are produced, we can be reasonably certain, by the very slow and indefinitely long-continued action of the poison. Its effects are, perhaps, functional, later altering the structure, which it finally subverts in the last stages of the disease.

Let us take an illustration drawn from acute disease. In traumatic tetanus we have a typical instance of a microbial toxin developed at the point of infection, entering the circulation, and coming in contact with all tissues and organs, but electing to strike its lethal blow upon the motor side of the nervous system. We find its selective action carried still further, singling out those segments of the motor apparatus which preside over the muscles of the neck and jaw, expending its initial force upon them, and affecting them most profoundly throughout the course of the disease.

Into the domain of psychological disease,

the researches of Regis and Chevalier Lauvaure have thrown a very important ray of light. Very logically taking the urine as a partial, though so far as it goes absolutely reliable, index of blood states, they found among other things that the urine of maniacal patients caused excitation, while that from melancholic patients caused depression and stupor, when injected into animals. These observations, if corroborated, have a tremendous bearing upon the pathology of insanity. They simply indicate, and, in fact, fall little short of proving what has been suspected by many alienists, that, in these opposite emotional states, there are toxins circulating in the blood, which overstimulate the cerebral functions on the one hand and depress them on the other to a pathological degree. These toxins are eliminated with the urine, and give to it the special toxic characters above referred to.

Voison and Person, on the other hand, studied the toxicity of the urine of epileptics upon guinea-pigs and rabbits. They found this toxicity diminished just before an attack, and increased after it; indicating that the epileptic paroxysm might be produced by the imperfect elimination of a convulsive toxin. Of course some of these facts are capable of another explanation, but in the present status of the entire question they must be regarded as of great importance.

Insanities due to the long-continued retention of excessive quantities of urea in the system are instances of brain disease produced by chemical products which are pres-

ent in toxic amounts because of defective elimination; while those due to the so-called gouty diathesis are due to perverted tissue-metabolism.

I will not occupy time by pursuing the evidence further, as I might very easily do. From the facts which I have cited, and which, I think, are in the main fairly well established, it is but an easy step to the further application of the theories which they seem to establish. It is easy to understand how many diseases of the nervous system, both organic and what are, by common sufferance, called functional in character, may be the results of the long-continued action of certain chemical products derived from some of the sources indicated. Their presence in the circulating fluid permits them to exercise increasing action upon the different parts of the nervous mechanism, and, by what may not inaptly be termed the law of their selective action or affinity, produce an insanity in one case, a locomotor ataxia in another, and a multiple neuritis (as in beri-beri) in still another; whether it be intestinal ptomaines, retention of effete products, or perverted metabolism, the physical and physiological conditions are ultimately the same. The opportunities for working out their specific effect are perfect and complete.

In conclusion, permit me to say that no one can be more conscious than myself of the imperfect manner in which this topic has been treated. My apology lies in the immensity of the field which I have attempted simply to outline, and in the obscurity which hangs around much of the

entire subject. If I have succeeded in stimulating thought and discussion in this direction, and in emphasizing the importance of a vast and fertile field for both clinical and laboratory research, I have accomplished my purpose.

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